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Chapter 14: Venous Thromboembolism

INTRODUCTION

- *Venous thromboembolism* (VTE) results from venous formation, manifesting as deep vein thrombosis (DVT) or pulmonary embolism (PE).

CLINICAL PRESENTATION

- Some patients with DVT are asymptomatic. Symptoms may include unilateral leg swelling, pain, tenderness, erythema, or warmth. Signs may include a palpable cord and a positive Homan's sign.
- PE symptoms may include cough, chest pain or tightness, shortness of breath, palpitations, hemoptysis, dizziness, or lightheadedness. Signs of PE include tachypnea, tachycardia, diaphoresis, cyanosis, and/or hypotension, with worse cases as shock or cardiovascular collapse.
- Postthrombotic syndrome may produce chronic lower extremity swelling, pain, tenderness, skin discoloration, and ulceration.

DIAGNOSIS

- Assessment focuses on identifying risk factors (increasing age, VTE, blood stasis, vascular injury hypercoagulability).
- Compression ultrasound (CUS) and computed tomography pulmonary angiography (CTPA) are used for initial suspected VTE evaluation.
- Ventilation-perfusion (V/Q) scan is an alternative in pregnancy and renal impairment.
- Clinical assessment checklists (eg, Wells score) assess the likelihood of DVT or PE.
- D-dimer is almost always elevated; <500 ng/mL (mcg/L) with Wells score helps rule out VTE.

TREATMENT

- Goals of Treatment: Initial goal—prevent VTE in at-risk populations. VTE treatment prevents thrombus extension and embolization, lowers recurrence risk, and prevents long-term complications (eg, postthrombotic syndrome, chronic thromboembolic pulmonary hypertension).

PREVENTION OF VTE

- Nonpharmacologic methods improve venous blood flow by mechanical means and include early ambulation, graduated compression stockings, intermittent pneumatic compression (IPC) devices, and inferior vena cava filters.
- Hospitalized and acutely ill medical patients at high VTE risk and low bleeding risk should receive prophylaxis with **low-dose unfractionated heparin** (**UFH**), **low-molecular-weight heparin** (**LMWH**), **fondaparinux**, or **rivaroxaban** during hospitalization or until fully ambulatory. Extended prophylaxis (up to 35 days) is recommended for patients with highest risk or prior VTE without bleeding risk. Routine pharmacologic prophylaxis is not needed for low-risk patients.
- Most patients undergoing general, gynecologic, cardiac, and vascular surgery should receive LMWH or low-dose UFH prophylaxis. If contraindicated, use IPCs or compression stockings.
- Recommended VTE prophylaxis following joint replacement surgery includes **aspirin**, adjusted-dose **warfarin**, **low-dose UFH**, **LMWH**,

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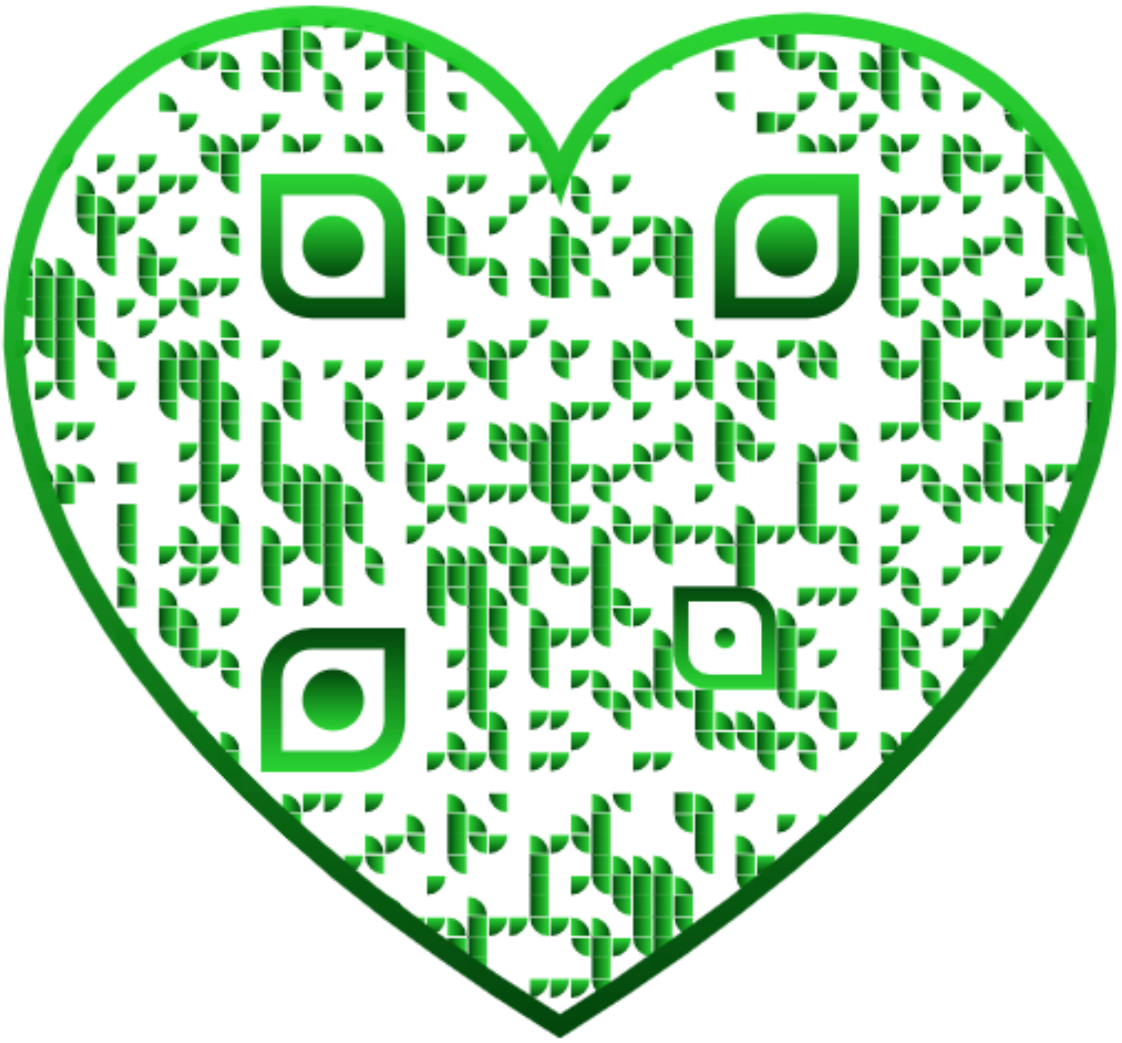


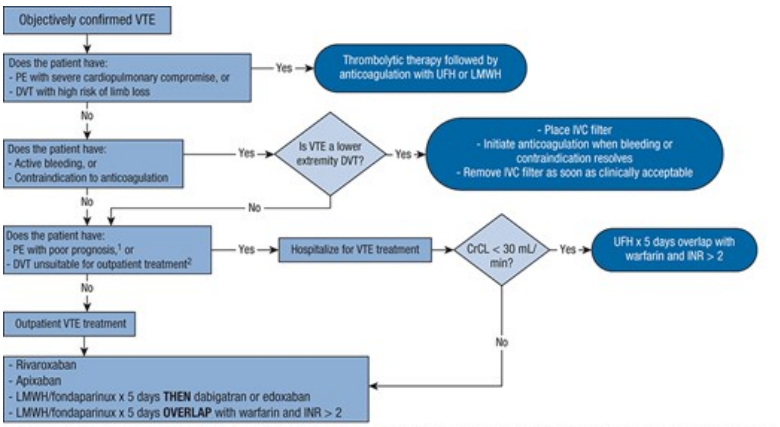
fondaparinux, **direct-acting oral anticoagulants (DOACs)** for ≥10 days.

- Prophylaxis should continue during increased VTE risk; guidelines support up to 42 days after major surgery. Most clinical trials support 15–42 days of prophylaxis after total knee or hip replacement surgery.
- High-risk patients with cancer (based on Khorana score) may receive LMWH, apixaban, or rivaroxaban.

GENERAL APPROACH TO TREATMENT OF VTE

- Anticoagulation is the primary treatment for VTE; DVT and PE are treated similarly (**Fig. 14-1**).
- After objective VTE confirmation, start rapid-acting anticoagulant promptly. Most patients with DVT and those with hemodynamically stable PE can be treated outpatient; unstable PE requires admission.
- Stable patients with DVT or PE with normal vital signs, low bleeding risk, and no uncontrolled comorbidities requiring hospitalization can be discharged early or treated entirely outpatient.
- Three months is standard initial anticoagulation duration for first VTE, including when linked to major transient or reversible risk factor (eg, surgery, hospitalization).
- Extended therapy prevents new VTE episodes. Consider >3 months for first unprovoked (idiopathic) VTE due to high recurrence rate. In patients with active cancer, therapy is rarely stopped.

FIGURE 14-1


Objectively confirmed VTE
Does the patient have:
- PE with severe cardiopulmonary compromise, or
- DVT with high risk of limb loss
Yes
Thrombolytic therapy followed by anticoagulation with UFH or LMWH
No
Does the patient have:
- Active bleeding, or
- Contraindication to anticoagulation
Yes
Is VTE a lower extremity DVT?
Yes
- Place IVC filter
- Initiate anticoagulation when bleeding or contraindication resolves
- Remove IVC filter as soon as clinically acceptable
No
No
Does the patient have:
- PE with poor prognosis,[1] or
- DVT unsuitable for outpatient treatment[2]
Yes
Hospitalize for VTE treatment
CrCL < 30 mL/min?
Yes
UFH x 5 days overlap with warfarin and INR > 2
No
Outpatient VTE treatment
No
- Rivaroxaban
- Apixaban
- LMWH/fondaparinux x 5 days THEN dabigatran or edoxaban
- LMWH/fondaparinux x 5 days OVERLAP with warfarin and INR > 2

Acute treatment of venous thromboembolism (VTE). CrCl, creatinine clearance via Cockcroft and Gault equation; DVT, deep vein thrombosis; INR, international normalized ratio; IVC, inferior vena cava; LMWH, low-molecular-weight heparin; PE, pulmonary embolism; UFH, unfractionated heparin; VTE, venous thromboembolism (includes DVT and PE).

[1]PESI score ≥86 points: age (1 pt for each year); male sex (10 pts); cancer (30 pts); heart failure (10 pts); COPD (10 pts); heart rate >110 bpm (20 pts); respiratory rate >30/min (20 pts); temperature <36°C (20 pts); altered mental status (60 pts); O_2 sat <90% (20 pts).
[2]Severe symptoms, renal impairment, inability to obtain or administer appropriate initial anticoagulant therapy, or high bleeding risk.

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NONPHARMACOLOGIC THERAPY

- Encourage ambulation as tolerated.
- Ambulation with graduated compression stockings reduces pain and swelling faster than strict bedrest without increasing embolization rate.
- IVC filters are reserved for patients with contraindications to anticoagulants from active bleeding.
- Thrombolysis or thrombectomy may be warranted in life- or limb-threatening DVT.

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PHARMACOLOGIC THERAPY

Direct Oral Anticoagulants (DOACs)

- **Rivaroxaban, apixaban,** and **edoxaban** are oral selective inhibitors of both free and clot-bound factor Xa and do not require antithrombin to exert their anticoagulant effect. **Dabigatran** is an oral selective, reversible, direct factor IIa (thrombin) inhibitor.
- See **Table 14-1** for DOAC indications and dosing. Use DOACs cautiously in renal dysfunction.
- Single-drug oral therapy with rivaroxaban or apixaban shows similar recurrent VTE rates as with warfarin overlapped with enoxaparin, with possibly less major bleeding. Both start with higher doses then transition to maintenance dosing, and need no routine monitoring; high cost may limit use.
- Edoxaban and dabigatran require >5 days of subcutaneous (SC) anticoagulation (UFH, LMWH, fondaparinux). Both were noninferior to warfarin for recurrent VTE; dabigatran caused similar major bleeding and edoxaban less. Dabigatran is not recommended in cancer-related VTE due to insufficient data.
- Bleeding is the most common DOAC adverse effect. Management includes supportive care and discontinuation. Idarucizumab (Praxbind) rapidly reverses dabigatran's anticoagulant effect in emergencies (eg, life-threatening bleeding, need for urgent surgical intervention). Recombinant coagulation factor Xa (also known as andexanet alfa; Andexxa) reverses life-threatening bleeding with rivaroxaban or apixaban. Avoid aspirin with DOACs; it nearly doubles bleeding rates; and should be avoided in most patients with VTE. All DOACs are P-gp substrates and are affected by P-gp inhibitors or inducers. Rivaroxaban and apixaban are affected by CYP3A4 inhibitors or inducers.

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TABLE 14-1

Approved Indications and Dosing for the Direct Oral Anticoagulants

Generic (Brand) Name	VTE Prophylaxis	Acute VTE Treatment	Reduction in Risk of Recurrent VTE in Patients at Continued Risk
Dabigatran (Pradaxa)[a]	Hip replacement surgery: 110 mg the first day beginning 1–4 hours after surgery once hemostasis is achieved, then 220 mg once daily for 28–35 days.	150 mg PO twice daily with or without food FOLLOWING at least 5 days of parenteral anticoagulant therapy	150 mg PO twice daily with or without food after previous treatment
Rivaroxaban (Xarelto)[b]	Hip or knee replacement surgery: 10 mg PO once daily with or without food beginning 6–10 hours after surgery once hemostasis is achieved and continuing for 12 (knee) to 35 (hip) days; acutely medically ill: 10 mg once daily with or without food in hospital and after discharge for 31–39 days	15 mg PO twice daily with food for days 1–21, then 20 mg PO once daily with food beginning on day 22	10 mg PO once daily with or without food after at least 6 months of treatment
Apixaban[c] (Eliquis)	Hip or knee replacement surgery: 2.5 mg PO twice daily with or without food beginning 12–24 hours after surgery and continuing for 12 (knee) or 35 (hip) days	10 mg PO twice daily with or without food on days 1–7, then 5 mg PO twice daily beginning on day 8	2.5 mg PO twice daily with or without food after at least 6 months of treatment
Edoxaban (Savaysa)	Not approved for use	60 mg PO once daily with or without food FOLLOWING at least 5 days of parenteral anticoagulant therapy; 30 mg once daily with CrCl 15–50 mL/min (0.25–0.83 mL/sec) or body weight ≤60 kg or who use certain P-gp inhibitors	Not approved for use

CrCl, creatinine clearance; P-gp, P-glycoprotein; PO, by mouth; VTE, venous thromboembolism.

[a]CrCl ≤ 30 mL/min or on dialysis; dosing recommendations cannot be provided.

[b]CrCl < 15 mL/min or on dialysis; not recommended.

[c]CrCl < 15 mL/min or on dialysis; not studied.

Low-Molecular-Weight Heparin

- LMWH fragments produced by chemical or enzymatic depolymerization of UFH are heterogeneous mixtures of sulfated glycosaminoglycans with approximately one-third the mean UFH molecular weight. LMWH prevents thrombus propagation by accelerating antithrombin activity similar to

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UFH.

- Administered SC in fixed or weight-based doses, LMWH is at least as effective as IV UFH for VTE and has largely replaced UFH due to improved pharmacokinetic/pharmacodynamic profiles and ease of use. Advantages include (1) predictable anticoagulation dose response, (2) improved SC bioavailability, (3) dose-independent clearance, (4) longer biologic half-life, (5) lower thrombocytopenia risk, and (6) less routine monitoring.
- Recommended doses (based on actual body weight) include:

  ✓ **Enoxaparin** (Lovenox): Acute DVT treatment with or without PE, 1 mg/kg SC every 12 hours or 1.5 mg/kg every 24 hours

  ✓ **Dalteparin** (Fragmin): Acute DVT treatment, 200 units/kg SC once daily or 100 units/kg SC twice daily (not FDA approved for this use in the United States). For VTE in cancer, 200 units/kg SC every 24 hours for 30 days, then 150 units SC every 24 hours; maximum dose: 18,000 units/day
- In patients without cancer, acute LMWH is usually transitioned to warfarin after 5 days of overlap with INR of ≥2.0 or used for 5 days before initiating dabigatran or edoxaban for acute VTE.
- Routine laboratory monitoring is unnecessary due to predictable SC response. Before therapy, obtain a baseline complete blood cell count (CBC) with platelet count and serum creatinine. Check CBC every 5–10 days during first 2 weeks, then every 2–4 weeks to detect occult bleeding. Anti–factor Xa is the main monitoring method but not needed in stable, uncomplicated patients. Monitoring may be considered with significant renal impairment, morbid obesity, or pregnancy.
- Bleeding is the most common LMWH adverse effect, but major bleeding may be less common than with UFH. If major bleeding occurs, IV protamine sulfate can be administered, but only partially neutralizes anticoagulant effect. Recommended dose: 1 mg per 1 mg of enoxaparin or 1 mg per 100 anti–factor Xa units of dalteparin administered in previous 8 hours; if bleeding persists, a second dose of 0.5 mg per 1 mg or 100 anti–factor Xa units can be given. Smaller doses can be used if LMWH was 8–12 hours earlier, but is not recommended if given >12 hours earlier.
- Thrombocytopenia can occur, but heparin-induced thrombocytopenia (HIT) incidence is one-third that of UFH. Osteoporosis risk is lower with LMWH.

Fondaparinux

- **Fondaparinux** (Arixtra) prevents thrombus generation and clot formation by indirectly inhibiting factor Xa via its interaction with antithrombin. Unlike UFH or LMWH, it inhibits only factor Xa.
- Safe and effective alternative to LMWH for acute VTE treatment, but is followed by long-term warfarin therapy.
- Dosed once daily SC by weight: 5 mg if <50 kg, 7.5 mg if 50–100 kg, and 10 mg if 100 kg.
- No routine coagulation testing is needed, but baseline kidney function must be checked; contraindicated if CrCl <30 mL/min (0.5 mL/sec).
- Bleeding is main adverse effect of fondaparinux. Obtain baseline and periodic CBC to detect occult bleeding and monitor for bleeding signs and symptoms daily. No specific antidote exists to reverse its activity.

Unfractionated Heparin

- **Unfractionated heparin** binds antithrombin, causing conformational change that enhances inhibition of factors IXa, Xa, XIIa, and IIa. This prevents thrombus growth and propagation, allowing endogenous thrombolytic systems to lyse clot. Because some patients respond poorly, IV UFH has largely been replaced by LMWH, fondaparinux, and DOACs, but remains useful in CrCl <30 mL/min (0.5 mL/sec) and unstable patients.
- For immediate and full anticoagulation, administer a weight-based IV loading dose followed by continuous IV infusion (**Table 14-2**). Subcutaneous UFH (333 units/kg then 250 units/kg every 12 hours) also provides adequate acute VTE treatment.
- Activated partial thromboplastin time (aPTT) is recommended for UFH monitoring if institution-specific therapeutic ranges are defined. Measure aPTT before therapy and 6 hours after initiation or dose change, adjusting UFH dose based on response and institution-specific therapeutic

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range.

- Monitor closely for bleeding. If major bleeding occurs, discontinue UFH immediately, identify and treat source, and give protamine sulfate by slow IV infusion (1 mg/100 units of UFH; maximum 50 mg).
- HIT is a rare, potentially fatal, immunologic reaction requiring immediate intervention. VTE is the most common complication of HIT; arterial thrombosis is less frequent. Thrombocytopenia is typical, but diagnosis requires serologic confirmation of heparin antibodies. Clinical prediction tools, such as the 4Ts score (*T*hrombocytopenia, *T*iming of platelet count fall or thrombosis, *T*hrombosis, o*T*her explanations for thrombocytopenia), improve predictive value of platelet count monitoring and heparin antibody testing. Discontinue all heparin if new thrombosis occurs with falling platelets and a moderate (4–5) or high (6–8) 4Ts score; and start alternative anticoagulation (direct thrombin inhibitor or fondaparinux).

TABLE 14-2

Weight-Based[a] Dosing for Unfractionated Heparin Administered by Continuous IV Infusion for Acute VTE

Initial Loading Dose	Maintenance Infusion Rate
80–100 units/kg	18 units/kg/h
Maximum = 10,000 units	Maximum = 2300 units/h
Activated Partial Thromboplastin Time (seconds)	***Dose Adjustment***
<37 (or anti–factor Xa <0.20 unit/mL [kU/L])	80 units/kg bolus, and then increase infusion by 4 units/kg/h
37–47 (or anti–factor Xa 0.20–0.29 unit/mL [kU/L])	40 units/kg bolus, and then increase infusion by 2 units/kg/h
48–71 (or anti–factor Xa 0.30–0.70 unit/mL [kU/L])	No change
72–93 (or anti–factor Xa 0.71–1 unit/mL [kU/L])	Decrease infusion by 1–2 units/kg/h
>93 (or anti–factor Xa >1 unit/mL [kU/L])	Hold infusion for 1 hour, and then decrease by 3 units/kg/h

[a]Use actual body weight for all calculations. Adjusted body weight may be used for obese patients (>130% of ideal body weight).

Warfarin

- **Warfarin** inhibits hepatic enzymes responsible for cyclic vitamin K interconversion. Reduced vitamin K is a cofactor for carboxylation of vitamin K–dependent coagulation factors II (prothrombin), VII, IX, and X and endogenous anticoagulant proteins C and S. Inhibiting reduced vitamin K produces less active proteins, suppressing clotting factor production, and initial thrombus formation and propagation. Anticoagulant effect onset depends on the clotting factor elimination half-lives (6 hours for factor VII and 72 hours for prothrombin); full effect requires ≥6 days.
- Due to slow onset, start warfarin concurrently with rapid-acting injectable anticoagulant, overlapping at least 5 days and until a therapeutic international normalized ratio (INR; usually ≥2) has been achieved for ≥24 hours.
- Guidelines for initiating warfarin therapy are given in **Fig. 14-2**. Initial dose: 5–10 mg orally daily; lower starting doses may be used in advanced age, malnutrition, liver disease, or heart failure. Avoid starting doses >10 mg.
- Warfarin is monitored by INR; target INR for VTE is 2.5 (range, 2–3). After an acute thromboembolic event, obtain baseline INR and CBC before warfarin and every 1–3 days (inpatient) and every 3–4 days (outpatient) until stabilized. Once dose response is established, check INR every 7–14

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days until it stabilizes, then ideally every 4–12 weeks.

- Maintenance dose changes should not be made more than every 3 days. Adjust weekly doses by calculating weekly dose and reducing or increasing it by 5%–20%; full effect may take 5–7 days.
- Bleeding (mild to life-threatening) is main adverse event. Warfarin does not cause bleeding directly, but exacerbates bleeding from lesions and minor sources. Risk increases with higher INR, so maintaining the INR within target range is essential:

  ✓ When the INR is 4.5–10 without bleeding, lower INR by withholding warfarin.

  ✓ For INR >10 without bleeding, give oral vitamin K (phytonadione 2.5 mg) but use cautiously in patients at high recurrent thromboembolic risk due to possible overcorrection.

- Major warfarin-related bleeding requires supportive care, rapid reversal with a four-factor prothrombin complex concentrate, and 5–10 mg of vitamin K given by slow IV injection.
- Rare, nonhemorrhagic adverse effects include: “purple toe” syndrome and skin necrosis.
- Due to numerous food–drug and drug–drug interactions with warfarin, close monitoring and additional INR checks are needed with medications or dietary vitamin K changes.

FIGURE 14-2

Initiation of warfarin therapy. INR, international normalized ratio; PT, prothrombin time.

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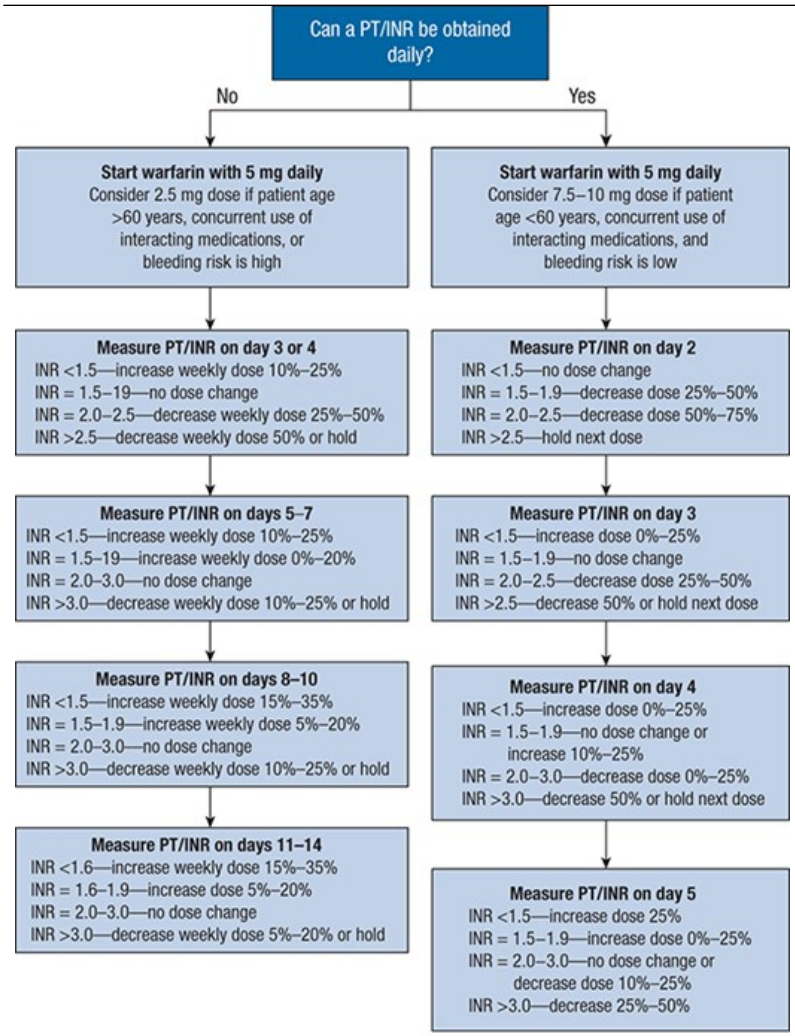

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Thrombolytics

- Thrombolytic agents are proteolytic enzymes that convert plasminogen to plasmin, which degrade fibrin.
- Most patients with VTE do not require thrombolytics. Use for limb-threatening DVT and select younger patients with symptomatic iliac/common femoral DVT within 14 days of symptom onset, good functional status, and low bleeding risk.
- Massive PE with hemodynamic compromise (hypotension or shock) warrants thrombolysis unless bleeding risk prohibits it.
- In massive PE manifested by shock and cardiovascular collapse (~5% of cases), thrombolytic therapy is indicated alongside aggressive interventions (volume expansion, vasopressor therapy, intubation, mechanical ventilation) to prevent progression to multisystem organ failure. Administer without delay, balancing PE mortality against bleeding risk.
- **Alteplase** (Activase) 100 mg IV over 2 hours is most common agent.
- Full-dose IV UFH should be administered before thrombolysis. During thrombolytic therapy, IV UFH may be continued or suspended; in the United States, it is usually suspended.
- After thrombolysis, measure aPTT. If <80 seconds, start UFH and adjust to therapeutic range. If >80 seconds, remeasure every 2–4 hours and start UFH once <80 seconds.

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EVALUATION OF THERAPEUTIC OUTCOMES

- Monitor symptom resolution, recurrent thrombosis, postthrombotic syndrome, and anticoagulant adverse effects.
- Monitor hemoglobin, hematocrit, and blood pressure to detect bleeding.
- Obtain baseline coagulation tests (aPTT, PT, INR) before therapy to guide management.
- For outpatients on DOACs or warfarin, assess medication adherence, other medications, health changes, bleeding/thromboembolic symptoms, and dietary vitamin K intake in warfarin users.

See Chapter 41, Venous Thromboembolism, authored by Daniel M. Witt, Nathan P. Clark, and Sara R. Vazquez, for a more detailed discussion of this topic.

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